Fatal pulmonary embolism update: 10 years of autopsy experience at an academic medical center

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Summary

Objective   To investigate the rate of death caused by pulmonary embolism (PE) and the antemortem performance in diagnosis and treatment of PE.

Design   A systematic search of cases involving fatal PE via PowerPath® (Sunquest) followed by chart review.

Setting   An academic medical centre located in San Diego, United States of America.

Participants   Postmortem cases with pathological findings of PE.

Main outcome measures   After data collection and collation, the data were subject to analysis.

Results   From 2002 to 2012, PE was identified as the mechanism of death in 108 of 982 cases (11%, 95% CI 9.01–12.99%) at an institution with an average autopsy rate of 30% ± 0.07%. Excluding cases where care was withheld (by advance directive) or unavailable, 29 of 108 were eligible for antemortem treatment for PE. In 31% (nine of 29) of these cases the diagnosis of PE was considered antemortem. Only three of 29 were given thrombolytics despite only one case being contraindicated.

Conclusion   The rate of PE-related death is consistent with most other autopsy series and major epidemiologic studies despite advances in system wide deep venous thrombosis prophylaxis. The results validate previous studies that this diagnosis is often missed but probably improving compared to historical standards. Even when the diagnosis is considered, however, thrombolytics are not routinely given, even without contraindications. The cause of this failure to treat may require further study with comparison to patients that were treated to determine the utilization of this treatment. It also underscores the continued difficulty in the diagnosis of this disease.

Introduction

A large acute pulmonary embolism (PE) is a catastrophic consequence of deep vein thrombosis. Relatively common, the incidence of PE is approximately 23 per 100,000 population annually in the United States.[1] It has been estimated that 1% of all patients admitted to hospitals die of acute PE, and 10% of all hospital deaths are PE-related.[2] Among patients with higher severity of disease, in-hospital mortality approaches 50%.[3] Meta-analysis of clinical records by VTE Impact Assessment Group in Europe (VITAE Group (EU)) estimated 295,982 deaths per annum in six developed European countries from PE with three quarters labelled hospital acquired. As per this analysis, only 7% were diagnosed antemortem.[4]

A review of recent literature reveals little more than four autopsy series over the last 30 years. In a retrospective 5-year review in 1989, Sandler et al.[5] (47% institution autopsy rate) found PE to be cause of death in 10% of autopsied patients (1979–1983), where only 3% of cases were suspected (no reported confidence intervals). In 1997, Baglin et al.[6] reviewed 400 consecutive autopsies (unknown institution autopsy rate or dates of review) and found 2.5% to be from PE (95%, CI 0.8–5.7%). Pineda et al.[7] in 2001 conducted a 5-year review of a large academic hospital from 1991 to 1996 (12.9% institution autopsy rate) and found that 9.1% died from PE (95% CI, 7–11%) with 30% receiving anticoagulation or thrombolysis (no differentiation offered between the two treatments). Alikhan et al.[8] in 2004 conducted a retrospective 10-year review from 1991 to 1996 (42% institution autopsy rate) and found that 5.2% died from PE. In 2011, Kopcke et al.[9] in a one-year retrospective review of death certificates and autopsies (27% autopsy rate) found 2.0% of deaths from PE (95%, CI 1.2–3.3%).

PE as a clinical entity often presents as a rapid and severe haemodynamic collapse leaving clinicians with little time to react. Thus public health efforts are typically directed to prevention of thrombosis in high-risk patients. In patients too unstable for radiographic evaluation, the diagnosis will have to be made based on clinical suspicion alone. Prior research shows that PE is one of the most common unrecognized diagnoses found at autopsy among ICU patients who suddenly expire.[10] Treatment for massive PE typically entails intravenous administration of thrombolytic agents (e.g. alteplase, etc.), while surgical thrombectomy is also performed at select centres. In the setting of cardiac arrest due to suspected PE, thrombolysis remains the treatment recommended in the 2010 ACLS guidelines[11] as there is no viable alternative.

The present study aims to quantify the performance at a single university medical centre with regard to the diagnosis and treatment of acute, haemodynamically significant PE. Autopsy records were used to identify cases of fatal PE, and chart review was done to indicate: (1) how often the diagnosis was recognized antemortem and (2) how often TPA was given in those cases where it would have been potentially beneficial.

Methods

Retrospective chart review was used to correlate autopsy records with clinical records. The PowerPath® (Sunquest, Tuscon, Arizona) pathology database was used to identify all patients autopsied at UC San Diego Medical Center for the 10 years prior to March 2012 whose primary cause of death was confirmed at autopsy to be PE. Using an automated search feature, the terms 'PE', 'pulmonary emboli' and 'pulmonary thromboembolism' were inputted to find records containing such terms. Clinical records, available electronically on EPIC® (Epic Inc., Verona, Wisconsin), were used to determine whether the diagnoses was recognized, and what treatments were given. Records were matched using demographic information and medical record numbers.

All patients with acute PE as the primary cause of death at autopsy were included. The pathologic criteria used to determine this were dependent on both of the following criteria: (1) gross evidence of an occlusive thrombus in the bifurcation of the pulmonary artery and (2) histologic evidence that this lesion was both organizing and associated with the vessel wall (Table 1).

Patients were excluded from the analysis if PE was not the mechanism of death, which generally excluded chronic or subacute cases of PE. Of those where PE was the mechanism, further subgrouping was categorized based on eligibility for treatment. Thus, any comfort care patients or patients who previously had advanced directive against

Table 1

Histologic findings in acute thrombi

Histology	
1.	Fibrin attachment to underlying vessel wall
2.	Organization with or without early recanalization
3.	Fibrin lamination (lines of Zahn)
4.	Elastic-type artery

Figure 1. Antemortem diagnosis (clinical).
Note: 32% (*n* = 9) of cases had PE in clinical differential diagnosis.

resuscitation or those who died outside of a healthcare setting were excluded from the final eligible for treatment group analysis. Paediatric and fetal cases were excluded entirely.

The diagnosis of PE was considered as recognized if the clinical notes indicated that the diagnosis was explicitly suspected on clinical grounds prior to the patient's death. Both electronic and paper charts were reviewed where necessary. Thrombolytics were noted to be given only if explicitly noted in the medical records; otherwise, it was assumed that they were not given. Thrombolytics were considered contraindicated if the patient had a condition that would likely be fatal if given: known intracranial haemorrhage, severe gastrointestinal or other non-compressible site of haemorrhage. Recent spinal surgery was not considered a contraindication, as we considered risk of death if untreated to outweigh potential risk of paralysis if treated.

Results

Over the last 10 years ending in March 2012, 108 out of 982 or 11% (95% CI 9.01–12.99%) of autopsied cases resulted in the diagnosis of PE as the mechanism of death. The institution has an average in-house autopsy rate of 30% (STD 0.07%) of all deaths (this does not include the average 10% of deaths that are claimed by County Medical Examiner for statutory reasons). Seventy-nine of these 108 cases were excluded as not eligible for treatment either because patient was receiving palliative care for terminal illness, had an advanced directive against resuscitation or died in a setting where medical treatment could not be initiated (e.g. pronounced dead at discovery with no resuscitation attempt). The remaining
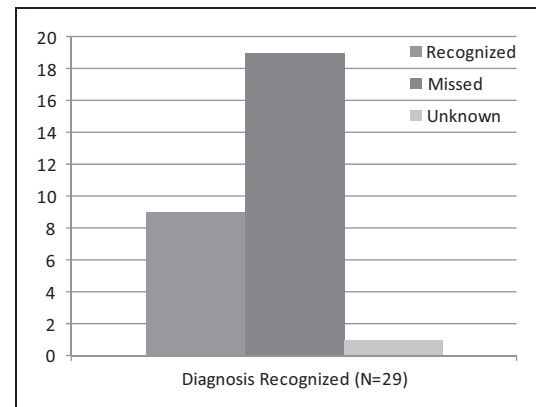
29 cases eligible for treatment, roughly a quarter of PE cases or 3% of total 982 autopsied deaths (95% CI 1.91–4.09%), were further reviewed.

The average age was 52 (STD 13). A slight predominance of male cases (62%) to female (38%) cases was seen. In 31% of these cases (*n* = 9), the diagnosis of PE was considered or 0.9% of overall panel (95% CI 0.33–1.57%) (see Figure 1). Three out of the 29 cases were given thrombolytic treatment with only a single case being contraindicated for treatment.

Discussion

This retrospective, single-centre study reveals trends both in incidence and in the diagnosis and treatment of major PE. First, the diagnosis continues to be difficult to recognize; however, this is improved compared to historic levels. Second, even when it is considered in the antemortem differential, thrombolytics are not routinely given, even in the absence of contraindications.

Regarding rate of PE, our data are similar to Sandler et al.[5] and Pineda et al.[7] which was found to be 10% and 9.1%, respectively. This differs from the findings of Baglin et al.,[6] Alikhan et al.[8] and Kopcke et al.[9] that estimate the rate is falling to levels between 2 and 5.2% Excluding Baglin et al.[6] and Kopcke et al.[9] from this group of analyses, because they were smaller studies where the former had 400 cases in an unknown time frame and the latter was a single-year

retrospective review, may offer a better comparison. Thus when compared to Alikhan et al.'s[8] review, which was also a ten-year retrospective autopsy review with a similar institutional autopsy rate, our data yielded approximately double their rate (5.2%). Interestingly, our rate approaches quadruple the rate of the findings of Baglin et al.[6] and Kopke et al.[9]; however, we suspect their studies due to the reasons listed above may not have sampled enough cases to obtain a true estimate. And although Alikhan et al.'s[8] review has approximately half the rate of what is seen at our institution, this could be accounted for by a number of possible variables that are more related to differences between institutions (e.g. their institution is in London and is part of a socialized medicine model).

With regard to antemortem diagnosis, the estimates were 3% around 1980 (as per Sandler et al.[5]). This was followed by Pineda et al.,[9] who found it to waver around 44.8% in the mid-1990s with a subsequent 30% receiving anticoagulation or thrombolysis (no differentiation offered). This is closer in keeping with the findings in our study which found 32% were diagnosed antemortem, which supports the hypothesis that diagnosis rates have improved since the early-1980s (i.e. Sandler et al.[5]). Conversely, the VITAE found that 7% were diagnosed antemortem in 2007. This is likely an underestimate of diagnosis rates because that collection of data sets did not expressly differentiate between patients who were on hospice care or who died outside of healthcare settings, or essentially an environment where providers are not searching for a diagnosis (as in palliative care settings). Additionally, that study is a meta-analysis from many sources, so although it makes valid findings, they are not suitable for comparison to our study.

Since so few cases received thrombolytic treatment in our review, we suspect that the disease is undertreated even when it is suspected. We did not count heparinization as definitive intervention as this is not a thrombolytic agent. It may seem puzzling that only three cases had thrombolysis attempted given they typically presented in extremis where it may be reasonable to attempt any potential treatment no matter the potential complication. The real rates of thrombolytic use at this institution cannot be inferred from these data; however, this data set is subject to the selection bias inherent in autopsy studies since we do not assess how many patients lived after being treated (thrombolytic efficacy as it were). As such, without comparison to those that make it to discharge, only limited conclusions can be offered. Previous randomized clinical trials have differed in the number of patients needed to treat with thrombolysis to obtain good results, i.e. patient living after hospital discharge. They suggest a range from 4.5 to 10 patients need to be treated for it to be successful.[12–14] To obtain those odds, however, the treatment needs to be attempted, a scenario that was uncommon in this series. Instead these patients were offered no specific treatment for PE or heparin only, despite current standard recommendations that heparin alone is not effective in major PE.[14]

This study has several limitations: the single-centre design and obvious selection bias limit generalizability. However, the study was performed in an academic tertiary care centre in which practices should be on par with other large hospitals. Additionally, other studies at similar institutions are available for comparison. Also, given that the study was retrospective chart review of potentially incomplete records an under- or over-estimate of rates is possible. Finally, we cannot provide any evidence on the efficacy of thrombolytics in massive PE given all patients had a fatal outcome.

Conclusion

An acute, massive PE can present a diagnostic challenge due to the rate and severity of decompensation seen in afflicted patients. Despite these challenges, the diagnosis rate is improved compared to historical standards. Additionally, this study re-affirms that major PE is still the gambit in the acutely decompensating patient that must be considered. We assert that in an acutely decompensating patient where PE is in the differential diagnosis and major contraindications are not evident, early use of thrombolytics should be considered.

References

1. Anderson FA Jr, Wheeler HB, Goldberg RJ, et al. A population based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. Arch Intern Med 1991;**151**:933–8

2. Lankeit M, Konstantinides S. Mortality risk assessment and the role of thrombolysis in pulmonary embolism. *Crit Care Clin* 2011;**27**(4):953–67

3. Choi WH, *et al*. The pulmonary embolism severity index in predicting the prognosis of patients with pulmonary embolism. *Korean J Intern Med* 2009;**24**:123–7

4. Cohen, *et al*. (VITAE Group). Venous thrombosis in Europe. *Thromb Haemost* 2007;**98**:756–764

5. Sandler, *et al*. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? *J R Soc Med* 1989;**82**:203–5

6. Baglin, *et al*. Fatal pulmonary embolism in hospitalized medical patients. *J Clin Path* 1997;**50**:609–18

7. Pineda LA, *et al*. Clinical suspicion of fatal pulmonary embolism. *Chest* 2001;**120**:791–5

8. Alikhan, *et al*. Fatal pulmonary embolism in hospitalized patients: a necropsy review. *J Clin Path* 2004;**57**:1254–7

9. Kopcke, *et al*. Mortality from pulmonary embolism is decreasing in hospital patients. *J R Soc Med* 2011;**104**:327–31

10. Podbregar M, *et al*. A triad algorithm for analysing individual ante- and post-mortem findings to improve the quality of intensive care. *Anaesth Intensive Care* 2011;**39**(6):1086–92

11. Neumar, *et al*. *Part 8: Adult advanced cardiac life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care*. American Heart Association. 2010

12. Er F, Nia AM, Gassanov N, *et al*. Impact of rescue-thrombolysis during cardiopulmonary resuscitation in patients with pulmonary embolism. *PLoS ONE* 2009;**4**(12):e8323

13. Wan S, *et al*. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism a meta-analysis of the randomized controlled trials. *Circulation* 2004;**110**: 744–9

14. Konstantinides, *et al*. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *New Eng J Med* 2002;**347**(15):1143